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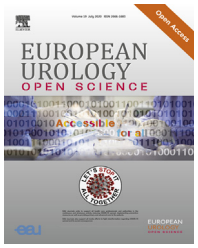

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Real-world Treatment Patterns and Overall Survival in Locally Advanced and Metastatic Urothelial Tract Cancer Patients Treated with Chemotherapy in Denmark in the Preimmunotherapy Era: A Nationwide, Population-based Study

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Abstract

Background: Real-world treatment patterns and survival outcomes of locally advanced, unresectable, and metastatic urinary tract cancer (mUTC) patients have not previously been studied in a nationwide, population-based cohort.
Objective: To describe treatment patterns and survival outcomes in mUTC patients treated in the real-world clinical setting.
Design, setting, and participants: This nationwide, population-based study included all mUTC patients initiating first-line chemotherapy at Danish oncology departments from January 2010 to March 2016. Data were retrospectively obtained from electronic medical records.
Outcome measurements and statistical analysis: Outcome measurements were descriptive. Kaplan-Meier was used for survival analysis.
Results and limitations: Of 952 patients included in the study, 46.2% initiated standard gemcitabine/cisplatin (GC) and 21.1% gemcitabine/carboplatin (CaG); the remaining patients initiated other treatment regimens. Median follow-up was 11.6 mo. The overall response rate and disease control rate were 43.0% and 61.7% in all patients, 51.4% and 69.1% in GC-treated patients, and 34.4% and 58.8% in CaG-treated patients, respectively. Median overall survival (OS) was 11.7 (95% confidence interval [CI]: 10.8–12.5) mo in all patients, 14.0 (95% CI: 12.5–15.5) mo in GC-treated patients, and 9.8 (95% CI: 8.7–10.9) mo in CaG-treated patients. Limitations include the retrospective study design.

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Conclusions: Real-world mUTC patients are older and less fit than patients enrolled in clinical trials; despite this, tumor responses and survival are comparable. Survival in our patient cohort is also comparable with that reported from other real-world studies in this patient group.

Patient summary: We studied treatment patterns and survival in urinary tract cancer patients receiving chemotherapy in the real-world clinical practice. Survival in our patient cohort was comparable with that reported from clinical trials and other real-world studies in this patient group.

1. Introduction

Urinary tract cancer (UTC) is defined as primary carcinomas of the renal pelvis, ureter, bladder, and urethra of different histologic subtypes. The most frequent tumor location is the bladder. Of the tumors, 90% are urothelial carcinomas and only a minority are squamous cell carcinomas, adenocarcinomas, small-cell neuroendocrine carcinomas, or other tumors of variant histologies [1,2].

According to European Association of Urology and European Society for Medical Oncology guidelines, cisplatin-based combination chemotherapy is the preferred first-line treatment in patients with locally advanced, unresectable, and metastatic UTC (mUTC) with gemcitabine/cisplatin (GC) and methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) being the most frequently used regimens [2–6]. Efficacy of GC and MVAC are noninferior to each other, but due to its more favorable toxicity profile, GC is widely accepted as the standard first-line treatment regimen [6]. However, approximately 50% of treated patients are considered cisplatin ineligible mainly due to renal insufficiency, poor performance status (PS), or comorbidities [7,8]. For years, recommended treatment for these patients has been carboplatin-based combination chemotherapy [2,9,10]. Median overall survival (OS) in clinical trials has been estimated to be 14, 15, and 9 mo for patients treated with GC, MVAC, and carboplatin/gemcitabine (CaG), respectively [6,9]. However, patients enrolled in clinical trials are generally younger and have less comorbidity than patients managed in routine clinical practice [11], and therefore survival estimates from clinical trials cannot be generalized to all clinical settings [12,13]. Recently, immune checkpoint inhibitors (ICIs) have been approved as a first-line treatment option in cisplatin-ineligible patients in Europe [14]. However, the use of first-line ICI is restricted to a subgroup of PD-L1–positive patients [2].

To optimize treatment of mUTC patients, there is a need for more valid data on treatment outcomes in the real-world clinical setting, something that has not been studied in a nationwide, population-based cohort so far [15–19].

We therefore conducted a large, nationwide, population-based cohort study in all mUTC patients in Denmark initiating first-line chemotherapy, in order to describe patient characteristics, treatment patterns, tumor response, and survival.

2. Patients and methods

2.1. Setting

Approximately 1100 patients are diagnosed with invasive (stage ≥ T1) UTC in Denmark each year [20]. An estimated 30% of patients have de novo muscle-invasive disease and 10–20% of patients with superficial tumors eventually progress to muscle-invasive disease [21], but the exact number of patients developing mUTC is unknown. Patients with mUTC are treated in one of six specialized uro-oncology departments. Danish residents are equally entitled to publicly financed health care including oncologic treatment. Privately funded health care services are limited and do not include oncologic treatment of UTC. All health care data are stored electronically ensuring high data coverage, with few patients lost to follow-up.

Treatment guidelines remained unchanged during the study period (from January 1, 2010 to March 31, 2016) [22]. According to these guidelines, cisplatin-eligible patients with creatinine clearance (CrCl) >60 ml/min were treated with standard GC every 3rd week (cisplatin 70 mg/m^2 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8), whereas patients with CrCl of 50–60 ml/min initiated GC split course (GC sc; cisplatin 70 mg/m^2 administered on days 1 and 2 and gemcitabine 1000 mg/m^2 on days 1 and 8). Cisplatin-ineligible patients were treated with a 3-wk schedule of CaG (carboplatin AUC 4.5–5.0 on day 1 and gemcitabine 1000 mg/m^2 on days 1 and 8); if not considered platinum eligible, patients could be treated with single-agent gemcitabine (gemcitabine 1200–1250 mg/m^2 on days 1 and 8) [22]. Patients with small-cell neuroendocrine carcinomas were treated with carboplatin/etoposide (CaEto; etoposide 100 mg/m^2 and carboplatin AUC 5 on day 1 every 3rd week) [22]. According to guidelines, a maximum of six cycles of treatment were administered.

ICIs were introduced in Denmark in 2018 as standard treatment for selected patients and therefore not a treatment option in the study period.

2.2. Study population and data collection

Patients were identified from treatment registers of the six oncology departments and included if they met the following criteria: histologically verified mUTC, and initiation of first-line chemotherapy at Danish oncology departments during the study period. The date of study inclusion was defined as the date of first chemotherapy administration.

Patients were included irrespective of histologic subtype, prior neoadjuvant/adjuvant chemotherapy, prior treatment in clinical protocol, or comorbidity including other malignancies.

Data were obtained from electronic medical records. Time of data collection was December 2017 for one center, mid 2018 for one center, and mid 2019 for the remaining four centers.

2.3. Definitions of characteristics of study participants and tumor response

Eastern Cooperative Oncology Group (ECOG) PS was reported from the consultation in which the decision of treatment regimen was made. Tumors were considered as urothelial carcinomas if that was the predominant histologic subtype. Squamous cell carcinomas and adenocarcinomas were only considered as such, if the tumors solely consisted of this histologic subtype. Tumors were registered as small-cell neuroendocrine carcinomas if that was the predominant histologic subtype. First-line chemotherapy was defined as the first chemotherapy regimen administered after the diagnosis of mUTC. Patients were categorized in treatment groups and compared according to the first-line chemotherapy regimen initiated.

Tumor responses were evaluated by local radiologists using computed tomography (CT) scans performed as part of routine clinical practice. We report on tumor responses observed at the end of first-line chemotherapy. The overall response rate (ORR) was defined as the proportion of patients who had a complete response (CR) or a partial response (PR) after therapy, whereas disease control rate (DCR) was defined as the proportion of patients who had CR, PR, or stable disease.

2.4. Statistical analysis

Study inclusion date was defined as the date of start of first-line chemotherapy. Time at risk was computed from study inclusion until death, date of last contact (if the patient was no longer receiving care at the oncology department), or date of data collection (if the patient was still receiving care in the oncology department), whichever occurred first. We used Kaplan-Meier analysis to construct survival curves and estimate OS for the entire patient cohort and according to first-line chemotherapy regimen initiated. In addition, we calculated OS separately for men and women aged $\geq$70 and $<$70 yr. SPSS version 25.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis.

The study was approved by the Danish Patient Safety Authorities (file no.: 3-3013-2222/1) and the Danish Data Protection Agency (file no.: 2012-58-0004), and was conducted according to the Declaration of Helsinki.

3. Results

3.1. Patient characteristics at the time of study inclusion

Of the 952 patients included in the study, 440 (46.2%) initiated GC as first-line treatment, 84 (8.8%) initiated GC sc, and 201 (21.1%) initiated CaG; the remaining patients initiated one of the other treatment options (Table 1). The median age at the initiation of first-line chemotherapy was 69 (interquartile range [IQR]: 63–75) yr in the total cohort, 67 (IQR: 61–71) yr in GC-treated patients, 72 (IQR: 66–76) yr in patients treated with CaG, and 76 (IQR: 70–78) yr in patients receiving single-agent gemcitabine. Patients were predominantly male. Of the patients, 69.5% had ECOG PS 0–1 and 14.7% PS 2–3. Of GC-treated patients, 75.9% had PS 0–1 and 7.9% PS 2–3; among CaG-treated patients, 60.7% and 21.4% had PS 0–1 and PS 2–3, respectively (Table 1). In the majority of patients (92.3%), the histologic subtype was urothelial carcinoma, except for patients treated with CaEto, in whom the dominant histologic subtype was small-cell neuroendocrine carcinoma (74.3%). Metastases were most commonly located in local lymph nodes (50.8%), distant lymph nodes (30.6%), and lungs (27.6%).

3.2. Tumor response

In all 952 patients, ORR was 43.0% and DCR was 61.7%. ORR and DCR were 51.4% and 69.1% in GC-treated patients and 34.4% and 58.8% in CaG-treated patients, respectively (Table 2).

3.3. Subsequent treatment lines

In the entire cohort, 303 patients (31.8%) received second-line treatment, most often vinflunine. Of GC-treated and GC sc–treated patients, 38.0% and 36.9%, respectively, had second-line treatment (in the form of vinflunine in 69.5% and 67.7% of patients, respectively). Among patients receiving CaG, 24.4% subsequently received second-line treatment, most frequently vinflunine (77.6%), and among those treated with single-agent gemcitabine, 18.5% received second-line treatment (51.7% vinflunine). The most commonly administered treatment regimen in 34.3% of CaEto-treated patients receiving subsequent second-line treatment was topotecan (50.0%). Of the 303 patients who received second-line treatment, 76 (25.1%) subsequently received third-line treatment, and of them, 14 (18.4%) also received fourth-line treatment.

3.4. Overall survival

Among the 952 patients with mUTC treated with first-line chemotherapy, 851 (89.4%) had died at the time of data collection after a median follow-up of 11.6 (IQR: 6.3–23.0) mo. Median OS was 11.7 (95% CI: 10.8–12.5) mo (Table 3 and Fig. 1). In patients treated with GC, median OS was 14.0 (95% CI: 12.5–15.5) mo; in patients receiving CaG, OS was 9.8 (95% CI: 8.7–10.9) mo, and in patients receiving single-agent gemcitabine, OS was 7.5 (95% CI: 6.3–8.7) mo. OS in patients receiving GC sc and CaEto was 13.0 (95% CI: 8.6–17.5) and 13.5 (95% CI: 7.5–19.4) mo, respectively. In the entire cohort, median OS in men and woman aged $\geq$70 yr was 11.0 (95% CI: 9.2–12.7) and 10.5 (95% CI: 8.7–12.4) mo, respectively; in men and women aged $<$70 yr, median OS was 12.4 (95% CI: 11.1–13.6) and 13.2 (95% CI: 10.8–15.5) mo, respectively.

4. Discussion

In this nationwide, population-based cohort study of mUTC patients treated in the real-world clinical setting at Danish oncology departments, we described patient characteristics, tumor response, and survival according to the first-line chemotherapy regimen initiated.

This is the first nationwide, population-based cohort study on treatment patterns and survival in mUTC patients. Complete inclusion of patients, the large patient number, as well as the completeness of tumor response data and nearly complete follow-up in terms of survival are major study strengths. Another strength is access to detailed data from electronic medical records, which minimizes the risk of misclassification and enables detailed description of patient characteristics and treatment outcomes.

Table 1 – Baseline characteristics of 952 patients with mUTC initiating first-line chemotherapy at Danish oncology departments during the period from January 1, 2010 to March 31, 2016

	All	GC	GC sc	CaG	Gem	CaEto	Other [a]
Patients, *n* (%)	952 (100.0)	440 (46.2)	84 (8.8)	201 (21.1)	157 (16.5)	35 (3.7)	35 (3.7)
Age, median (IQR)	69 (63–75)	67 (61–71)	68 (63–73)	72 (66–76)	76 (70–78)	69 (63–76)	63 (59–71)
Gender, *n* (%)							
Male	686 (72.1)	339 (77.0)	64 (76.2)	131 (65.2)	104 (66.2)	25 (71.4)	23 (65.7)
Female	266 (27.9)	101 (23.0)	20 (23.8)	70 (34.8)	53 (33.8)	10 (28.6)	12 (34.3)
ECOG PS, *n* (%)							
0	341 (35.8)	205 (46.6)	35 (41.7)	32 (15.9)	33 (21.0)	20 (57.1)	16 (45.7)
1	321 (33.7)	129 (29.3)	34 (40.5)	90 (44.8)	48 (30.6)	7 (20.0)	13 (37.1)
2	135 (14.2)	34 (7.7)	4 (4.8)	42 (20.9)	47 (29.9)	5 (14.3)	3 (8.6)
3	5 (0.5)	1 (0.2)	0 (0.0)	1 (0.5)	3 (1.9)	0 (0.0)	0 (0.0)
Unknown	150 (15.8)	71 (16.1)	11 (13.1)	36 (17.9)	26 (16.6)	3 (8.6)	3 (8.6)
Histology, *n* (%)							
UC [b]	879 (92.3)	414 (94.1)	79 (94.0)	194 (96.5)	154 (98.0)	8 (22.9)	30 (85.7)
SCC	27 (2.8)	14 (3.2)	4 (4.8)	5 (2.5)	2 (1.3)	0 (0.0)	2 (5.7)
Adenocarcinoma	10 (1.1)	7 (1.6)	1 (1.2)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
SCN carcinoma	29 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (74.3)	3 (8.6)
Other	5 (0.5)	4 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Unknown	2 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)
Primary tumor location, *n* (%)							
Upper urinary tract	168 (17.6)	47 (10.7)	27 (32.1)	42 (20.9)	44 (28.0)	1 (2.9)	7 (20.0)
Bladder	767 (80.6)	382 (86.8)	56 (66.7)	155 (77.1)	113 (72.0)	34 (97.1)	27 (77.1)
Urethra	14 (1.5)	9 (2.0)	1 (1.2)	3 (1.5)	0 (0.0)	0 (0.0)	1 (2.9)
Unknown	3 (0.3)	2 (0.6)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
TNM stage [c]							
T4bN0M0	66 (6.9)	32 (7.3)	6 (7.1)	8 (4.0)	19 (12.1)	1 (2.9)	0 (0.0)
Any T, N+, M0	186 (19.5)	92 (20.9)	25 (29.8)	26 (12.9)	31 (19.7)	5 (14.3)	7 (20.0)
Any T, Any N, M1	650 (68.3)	297 (67.5)	48 (57.1)	160 (79.6)	101 (64.3)	18 (51.4)	26 (74.3)
Any T, Any N, Mx	20 (2.1)	12 (2.7)	1 (1.2)	3 (1.5)	2 (1.3)	1 (2.9)	1 (2.9)
Unknown	30 (3.2)	7 (1.6)	4 (4.8)	4 (2.0)	4 (2.5)	10 (28.6)	1 (2.9)
Metastatic sites, *n* (%)							
Local LN [d]	484 (50.8)	232 (52,7)	46 (54.8)	92 (45.8)	82 (52.2)	14 (40.0)	18 (51.4)
Distant LN [e]	291 (30.6)	145 (33.0)	15 (17.9)	82 (40.8)	34 (21.7)	5 (14.3)	10 (28.6)
Lungs	263 (27.6)	114 (25.9)	18 (21.4)	62 (30.8)	52 (33.1)	10 (28.6)	7 (20.0)
Liver	131 (13.8)	52 (11.8)	11 (13.1)	34 (16.9)	23 (14.6)	8 (22.9)	3 (8.6)
Bone	148 (15.5)	71 (16.1)	12 (14.3)	37 (18.4)	19 (12.1)	6 (17.1)	3 (8.6)
Brain	5 (0.5)	1 (0.2)	1 (1.2)	1 (0.5)	2 (1.3)	0 (0.0)	0 (0.0)
Other	129 (13.6)	48 (10.9)	13 (15.5)	36 (17.9)	21 (13.4)	4 (11.4)	7 (20.0)
Prior treatment, *n* (%)							
Intravesical therapy	63 (6.6)	26 (5.9)	4 (4.8)	18 (9.0)	12 (7.6)	0 (0.0)	3 (8.6)
NAC	42 (4.4)	9 (2.0)	2 (2.4)	14 (7.0)	3 (1.9)	5 (14.3)	9 (25.7)
Cystectomy	269 (28.3)	134 (30.5)	27 (32.1)	46 (22.9)	42 (26.8)	6 (17.1)	14 (40.0)
NU	110 (11.6)	24 (5.5)	21 (25.0)	32 (15.9)	27 (17.2)	1 (2.9)	5 (14.3)
Curative RT	62 (6.5)	14 (3.2)	2 (2.4)	31 (15.4)	9 (5.7)	1 (2.9)	5 (14.3)

CaEto = carboplatin/etoposide; CaG = gemcitabine/carboplatin; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine/cisplatin; GC sc = gemcitabine/cisplatin split course; Gem = gemcitabine; IQR = interquartile range; LN = lymph nodes; mUTC = metastatic urinary tract cancer; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin; NAC = neoadjuvant chemotherapy; NU = nephroureterectomy; RT = radiotherapy; SCC = squamous cell carcinoma; SCN carcinoma = small-cell neuroendocrine carcinoma; TNM = tumor, node, metastasis; UC = urothelial carcinoma.

[a] Other treatment regimens include MVAC, vinflunine/gemcitabine, cisplatin/gemcitabine/lapatinib, paclitaxel/carboplatin, paclitaxel/gemcitabine, and docetaxel/cisplatin/5-FU (include protocol treatment).

[b] Predominant histologic subtype.

[c] At the start of first-line chemotherapy.

[d] Lymph nodes located in the abdomen.

[e] Lymph nodes located outside the abdomen.

The median age of patients included in this study was considerably higher than that of patients with mUTC in previous clinical trials [5,23]. Accordingly, PS of patients included in clinical trials were superior to that of patients included in this real-world study [5,23]. These findings are in line with previous studies describing patients enrolled in clinical trials as younger and fitter than those treated in routine clinical practice [12,13].

Most patients in our study received cisplatin-based chemotherapy; a considerable proportion of the patients received GC sc. This treatment regimen is used in Denmark for patients with CrCl 50–60 ml/min and no other contra-indications for cisplatin. This Danish practice is likely to explain the widespread use of cisplatin in our patient population, which exceeds that of other real-world settings [24].

Contrary to what we expected, the CR rate among GC-treated patients in our study was higher than what was reported among GC-treated patients in previous clinical trials [5,23]. This might be explained by the application of

Table 2 – Tumor responses at the end of first-line chemotherapy according to treatment type in 952 patients with locally advanced, unresectable, and metastatic urinary tract cancer initiating first-line chemotherapy from January 1, 2010 to March 31, 2016

Tumor response	All	GC	GC sc	CaG	Gem	CaEto	Other [a]
Complete response, *n* (%)	96 (10.1)	66 (15.0)	9 (10.7)	11 (5.5)	5 (3.2)	4 (11.4)	1 (2.9)
Partial response, *n* (%)	313 (32.9)	160 (36.4)	33 (39.3)	58 (28.9)	37 (23.6)	13 (37.1)	12 (34.3)
Stable disease, *n* (%)	178 (18.7)	78 (17.7)	10 (11.9)	49 (24.4)	25 (15.9)	9 (25.7)	7 (20.0)
Progressive disease, *n* (%)	233 (24.5)	88 (20.0)	20 (23.8)	50 (24.9)	56 (35.7)	8 (22.9)	11 (31.4)
Unknown, *n* (%) [b]	132 (13.9)	48 (10.9)	12 (14.3)	33 (16.4)	34 (21.7)	1 (2.9)	4 (11.4)

CaEto = carboplatin/etoposide; CaG = gemcitabine/carboplatin; GC = gemcitabine/cisplatin; GC sc = gemcitabine/cisplatin split course; Gem = gemcitabine; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin.
[a] Other treatment regimens include MVAC, vinflunine/gemcitabine, cisplatin/gemcitabine/lapatinib, paclitaxel/carboplatin, paclitaxel/gemcitabine, and docetaxel/cisplatin/5-FU (include protocol treatment).
[b] Treatment responses unknown due to scans not performed after the last cycle of chemotherapy.

Table 3 – Median overall survival according to treatment type in 952 patients with locally advanced, unresectable, and metastatic urinary tract cancer initiating first-line chemotherapy from January 1, 2010 to March 31, 2016

	No. of patients	Median OS, mo (95% CI)
All	952	11.7 (10.8–12.5)
GC	440	14.0 (12.5–15.5)
GC sc	84	13.0 (8.6–17.5)
CaG	201	9.8 (8.7–10.9)
Gem	157	7.5 (6.3–8.7)
CaEto	35	13.5 (7.5–19.4)
Other [a]	35	13.4 (9.4–17.4)

CaEto = carboplatin/etoposide; CaG = gemcitabine/carboplatin; GC = gemcitabine/cisplatin; GC sc = gemcitabine/cisplatin split course; Gem = gemcitabine; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin; OS = overall survival.
[a] Other treatment regimens include MVAC, vinflunine/gemcitabine, cisplatin/gemcitabine/lapatinib, paclitaxel/carboplatin, paclitaxel/gemcitabine, and docetaxel/cisplatin/5-FU (include protocol treatment).

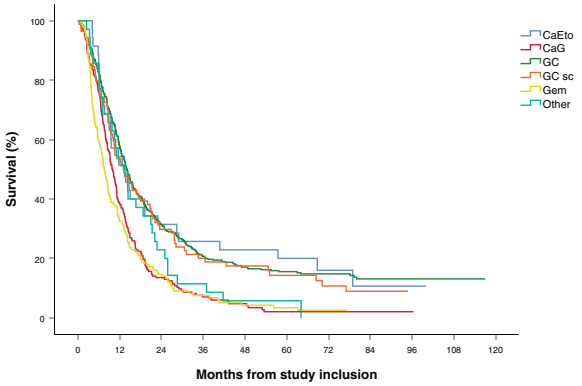

Fig. 1 – Overall survival according to treatment type in 952 patients with locally advanced, unresectable, and metastatic urinary tract cancer initiating first-line chemotherapy from January 1, 2010 to March 31, 2016.
Other treatment regimens include MVAC, vinflunine/gemcitabine, cisplatin/gemcitabine/lapatinib, paclitaxel/carboplatin, paclitaxel/gemcitabine, and docetaxel/cisplatin/5-FU (include protocol treatment). CaEto = carboplatin/etoposide; CaG = gemcitabine/carboplatin; GC = gemcitabine/cisplatin; GC sc = gemcitabine/cisplatin split course; Gem = gemcitabine; MVAC = methotrexate/vinblastine/doxorubicin/cisplatin.

stricter criteria for CR in clinical trials than in real-world settings [5,23]. However, tumor response among GC-treated patients was also better in our study than what has previously been demonstrated in a real-world setting in the study by Niegisch et al [19] (CR rate 12%; Table 4).

OS among patients treated with GC (including GC sc) and CaG was comparable with the results from two clinical trials [6,9]. This is surprising, as survival is generally better in clinical trials, but might be explained by the introduction of second-line treatment after the clinical trials were carried out. In our patient cohort, a considerable number of patients received second-line treatment regardless of first-line chemotherapy regimen and a minor proportion of patients received subsequent lines of treatment.

Survival in our study exceeds that of several other real-world studies on mUTC patients (Table 4): Galsky et al [16] reported a median OS of 8.5 mo in the entire cohort of mUTC patients and 12.1 mo in cisplatin-treated patients. However, patients in the Galsky et al's [16] study were considerably older than the patients in the present study, which might explain the differences in survival. Survival was also inferior in the study by Robinson et al [17], which might be partly explained by the study inclusion period (1994–2008), which was before the introduction of second-line treatment options. Other real-world studies have demonstrated survival superior to what we demonstrated [15,19]. This might be explained by a more favorable distribution of risk factors (age and PS) in these studies than in ours. To summarize these findings, survival in real-world studies seems to be associated with age and PS of the cohorts. In Table 4, results from previously conducted real-world studies and clinical trials in mUTC patients are summarized.

In our study population, 35 patients initiated first-line CaEto; in the majority of these patients small-cell neuroendocrine carcinoma was the predominant histologic subtype. Median OS in CaEto-treated patients was 13.5 (95% CI: 7.5–19.4) mo, which is in line with a previous finding in this rare subgroup of mUTC patients [25].

Although treatment options for mUTC have changed with the introduction of ICIs, only a minority of patients are eligible for this treatment option in the first-line setting, and therefore valid data from a real-world setting on patients treated with chemotherapy are still highly relevant.

The high number of patients receiving single-agent gemcitabine indicates that many mUTC patients are considered ineligible not only for cisplatin but also for carboplatin. Some of these patients might have benefitted

Table 4 – Summary of the results of three clinical trials and five previously conducted real-world studies on mUTC patients

	Bamias (2018) [15]	Galsky (2018) [16]	Robinson (2017) [17]	Fisher (2018) [18]	Niegisch (2018) [19]	This study	von der Maase (2000) [5]	Bellmunt (2012) [23]	De Santis (2012) [9]
Type of study (real-world studies vs clinical trials)	RW study	RW study	RW study	RW study	RW study	RW study	Clinical trial	Clinical trial	Clinical trial
No. of pts	1333	717	710	321	435	952	203	314	88
Age (median)	67.6	76 [a]	67	–	69	69	63	61	71
ECOG PS (%)									
0	26.0	–	–	–	28.7	35.8	– [b]	54.5	17.0
1	38.8	–	–	–	50.1	33.7	– [b]	45.5	42.0
≥2	13.9	–	–	–	14.3	14.7	– [b]	0.0	40.9
1L treatment regimen (%)									
Cisplatin based	50.2	26.8	54.5	37.7	71.0	55.0	100	100	0.0
GC	–	21.3	36.8	26.5	63.4	46.2	100	100	0.0
Non–cisplatin based	49.8	73.2	45.5	62.3	29.0	45.0	0.0	0.0	100
CaG (%)	–	31.5	13.5	36.8	10.8	21.1	0.0	0.0	100
ORR (CR/PR), (%)									
All pts	–	–	–	–	34 (11/22) [c]	43.0 (10.1/32.9)	49.4 (12.2/37.2) [c]	43.6 (11.1/32.5) [c]	42.0 (3.4/38.6) [c]
Cisplatin-treated pts	–	–	–	–	–	51.1 (14.3/36.8)	49.4 (12.2/37.2) [c]	43.6 (11.1/32.5) [c]	–
GC-treated pts	–	–	–	–	35 (12/23) [c]	51.4 (15.0/36.4)	49.4 (12.2/37.2) [c]	43.6 (11.1/32.5)[c]	–
CaG-treated pts	–	–	–	–	–	34.3 (5.5/28.9)	–	–	42.0 (3.4/38.6) [c]
Median OS (mo)									
All pts	–	8.5	9	11.0	16.1	11.7	13.8	12.7	–
Cisplatin-treated pts	18	12.1	–	13.3	–	–	13.8	12.7	–
GC-treated pts	–	–	10.0	–	17.7	14.0 [d]	13.8	12.7	–
Carboplatin-treated pts	12.5	–	–	10.6	–	9.8	–	–	–
CaG-treated pts	–	–	7.4	–	–	9.8	–	–	–

CaG = gemcitabine/carboplatin; CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; GC = gemcitabine/cisplatin; 1 L = first line; mUTC = metastatic urinary tract cancer; ORR = overall response rate; OS = overall survival; PR = partial response; pts = patients; RW = real world.

[a] Median age at diagnosis of metastatic disease.

[b] Performance status reported as Karnofsky performance status.

[c] Best overall response rate.

[d] Median OS for patients receiving standard GC.

from ICIs in the current clinical setting; yet, this finding highlights the need for the development of new therapeutic approaches.

Our study includes only patients initiating first-line chemotherapy. An unknown number of mUTC patients are found ineligible for systemic oncologic treatment at the time of diagnosis. Efforts must be taken to characterize this patient group and the reasons for treatment ineligibility, to try to enable treatment for these patients.

This study has certain limitations. Owing to the retrospective study design, missing data appear, particularly regarding ECOG PS. No data on renal function, comorbidities, laboratory values, toxicities, progression, and tumor response at different time points were registered, which is another shortcoming of the study. Finally, we cannot completely exclude the possibility of an imaging bias affecting our ORR, although this bias is likely to be of minor importance only. Radiologists at Danish hospitals have access to electronic medical records but are provided little patient information before evaluation of scans.

5. Conclusions

Patients with mUTC treated in the real-world clinical setting are older and less fit than patients included in clinical trials. Despite this, tumor responses and survival are comparable with those of patients enrolled in clinical trials. Survival in our patient cohort is also comparable with the survival outcomes in previously conducted real-world studies on mUTC patients.

Author contributions: Lise H. Omland had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CRediT authorship contribution statement

Lise H. Omland: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing, Investigation, Methodology, Project administration. **Henriette Lindberg:** Conceptualization, Data curation, Investigation, Methodology. **Andreas Carus:** Data curation, Investigation, Methodology. **Anne Birgitte Als:** Data curation, Investigation, Methodology. **Niels Viggo Jensen:** Data curation, Investigation, Methodology. **Gry A. Taarnhøj:** Formal analysis, Investigation, Methodology. **Redas Trepiakas:** Data curation, Investigation, Methodology. **Charlotte Suetta:** Supervision. **Lars H. Omland:** Formal analysis, Software, Validation, Visualization. **Helle Pappot:** Conceptualization, Formal analysis, Funding acquisition, Supervision, Software, Resources, Investigation, Methodology, Project administration.

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